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ABSTRACT

Using the Corey approach, retrosynthetic/synthetic schemes for six organic molecules of increasing complexity were programmed and tested in a module designed for a fourth year undergraduate course. A portion of a simple synthesis is presented and analyzed. Problems encountered were discussed and potential solutions are proposed. The module was evaluated by both instructor and student input and it is concluded that it serves to enhance understanding of and develop skill in the design of organic synthesis. (Author/JEG)

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COMPUTER-ASSISTED INSTRUCTION IN ORGANIC SYNTHESIS

BY

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COMPUTER-ASSISTED INSTRUCTION IN ORGANIC SYNTHESIS

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Abstract: A module useful in the instruction of organic synthesis was developed. Using the Corey approach, retrosynthetic/synthetic schemes for six organic molecules of increasing complexity were programmed and tested in a fourth-year undergraduate course. A portion of a simple synthesis is presented and analyzed. Problems encountered are discussed and potential solutions are proposed. The module was evaluated by both instructor and student input and it is concluded that it serves to enhance understanding of and develop skill in the design of organic synthesis.

Introduction:

Response to a definition of the term organic synthesis may vary from "the fruits of organic gardening" to "the operation of an oil refinery" and depends on the background of the respondent. In very general terms, organic synthesis is the preparation of carbon-containing molecules of varying complexity from simple components by a series of rational procedures. Very loosely, this can be translated as "fooling around with nature" since most simple molecules arise from natural sources, e.g. oil, coal, plants. We are of course highly dependent on these resources for our material (e.g. clothing), health (e.g. drugs), and energy (e.g. gasoline) needs. In view of the increasing scarcity of these resources, we need reliable, specific, and economic organic syntheses in order to meet our future needs.

Therefore, instruction in organic synthesis is a significant component of the education of a chemistry student. In our department, the undergraduate is widely exposed to this subject as practised in academic and fine chemical (e.g. pharmaceutical) laboratories as well as in large-scale industrial plants.

Fig. 1 ORGANIC SYNTHESIS IN THE CLASSROOM. CIRCA 1968
1. Myriad of Chemical Reactions
2. Information Storage by and Retrieval from Human Mind
3. Uncorrelated, Undigested Facts
4. Attempt to cover "everything"
5. Rote Learning
"Where is the wisdom we have lost in knowledge? Where is the knowledge we have lost in information?" T.S. Eliot

Fig. 2 ORGANIC SYNTHESIS IN THE CLASSROOM. CIRCA 1978
1. Synthesis of Selected Molecules
2. Practical Approaches, Alternate Routes
3. Highlight Important Chemical Reactions
4. Extensive Secondary and Tertiary Literature Base
5. Development of Useful Data Bank - Responsibility of Student
6. Take-away exams

A decade ago, instruction in organic synthesis (Fig. 1) was based on committing to memory a large amount of factual information, an ever-increasing tower of building blocks which were poorly interconnected and difficult to assimilate and correlate. An attempt was made to cover "everything" and examinations were regurgitations of rote learning. The modern approach to synthesis (Fig. 2) is to show how chemists go about constructing complex molecules by using a limited number of carefully selected cases. Alternate routes to a given target molecule are desirable to illustrate conceptual and practical differences. Instead of a myriad of reactions to memorize, the student learns a few important processes whose ramifications he studies outside of the classroom in the extensive secondary and tertiary literature now available. Therefrom, the student establishes a data bank of reactions which he uses for non-supervised, take-away examinations. In the future, points 4 and 5 of Fig. 2 will no doubt become the responsibility of computers.

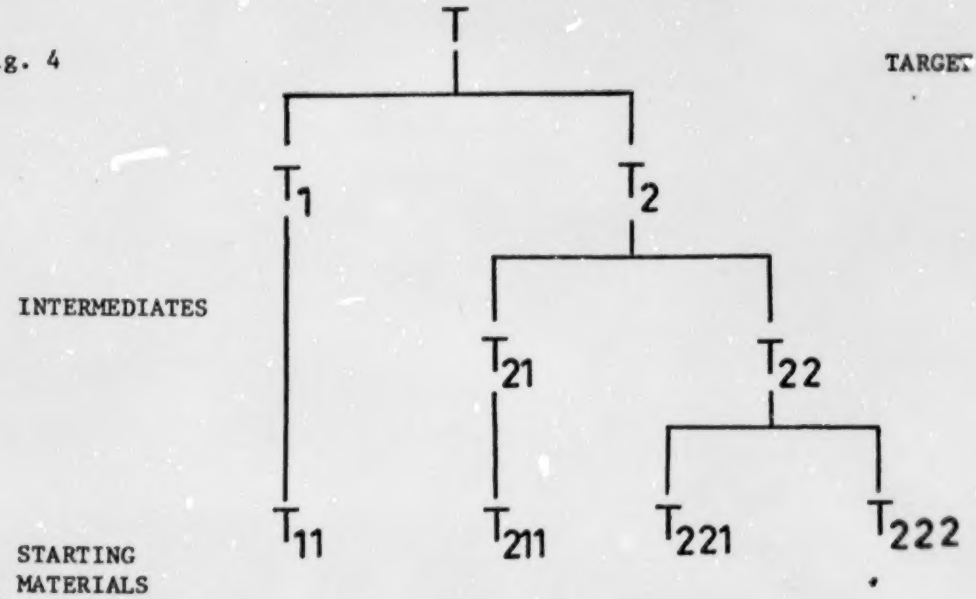
Corey [2] is responsible for the initial developments in computer-assisted organic synthesis. His program (LHASA) and more recent independent versions (PLATO [3], SYNCHEM [4]) are highly sophisticated aids for planning of complex syntheses. The COMIT Project presented the opportunity to develop a comparatively simple module to be used for undergraduate instruction.

Fig. 3 OBJECTIVES
1. To enhance understanding of principles of organic synthesis design
2. To develop skill and confidence in planning organic synthesis
3. To reinforce concepts taught in the classroom
4. To allow self-paced approach
5. To provide for constant, individualized evaluation
6. To assist students at several levels of proficiency

Objectives and Methods

In devising the Organic Synthesis Module (hereafter, ORGSYN), we set objectives which require no elaboration (Fig. 3). The method we used is based on the Corey model of Retrosynthetic Analysis [1]. (Fig. 4) A given target molecule (T) chosen for synthesis is dissected into a set of intermediates (T_1 and T_2) which are viable precursors of T by a single real (laboratory) chemical reaction. Iteration of this procedure for each intermediate leads to a "tree" of further intermediates, e.g. $T_2 \rightarrow T_{21}$ and T_{22}, until simplication of the hierarchy results in molecules that are commercially available. These are our starting materials, e.g. T_{11}, T_{211}, T_{221}, T_{222}. Thus the overall analysis, target to starting materials, is a process of working backwards relative to real laboratory experimentation.

Fig. 4



In ORGSYN, six target molecules (T) of increasing complexity were subjected to Retrosynthetic Analysis. These were 2-heptanol, iso-butylbenzene, 1-phenyl-3-pentanone, α-curcumene, lavandulol, and cis-jasmone [1]. For any given T, we restricted ourselves to three first-hierarchial intermediates T_1, T_2, T_3 which we hoped correctly predicted the most likely dissections students would pursue. Once an intermediate (T_1) was correctly identified, the student was asked to specify the reaction environment chosen from tables of reagents, solvents, and temperatures under which T_1 could be converted into T, i.e. to approximate actual laboratory conditions (extracted from the literature) for this conversion. This cyclical process was continued until the student received the message that a given target (e.g. T_{11}) was a starting material. Since ORGSYN was programmed in APL, communication required no knowledge of computer language.

The initial phases of a simple synthesis in ORGSYN with appropriate explanations are illustrated in Figs. 5 and 6.

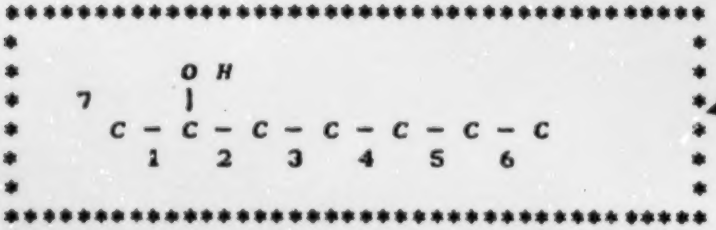
Fig. 5

```
**********************************************
*                                            *
*          O H                               *
*   7      |                                  *
*     C - C - C - C - C - C - C                *
*       1   2   3   4   5   6                 *
*                                            *
**********************************************
```

INTRODUCTORY REMARKS

Above is the graphic of the target molecule. In each graphic, carefully note the number used to label a bond. The number is either aligned vertically or horizontally with only one bond or an arrow is used. Some diagrams get a little cluttered. When entering more than one bond number, separate each with a blank. If no bond is to be broken (eg in the case of bond order changes), enter a zero (0).
PRESS ENTER

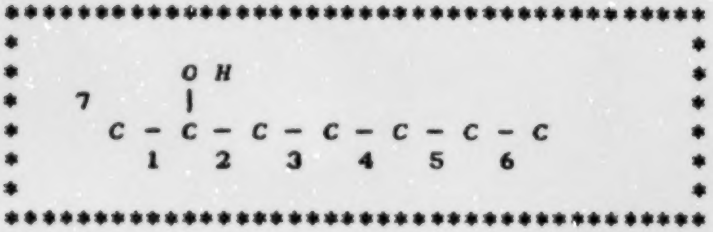
Fig. 5 continued



TARGET MOLECULE (T)

SUBSTANCE: 2-Heptanol IS THE TARGET MOLECULE
ENTER BOND NUMBER(S) TO BE BROKEN
2
NO, PRESS ENTER TO TRY AGAIN

REJECTED BOND 2 CLEAVAGE

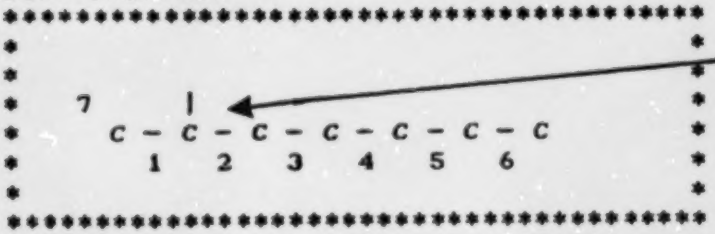


SUBSTANCE: 2-Heptanol IS THE TARGET MOLECULE
ENTER BOND NUMBER(S) TO BE BROKEN
7

ALLOWED BOND 7 CLEAVAGE

GOOD, THE NEXT STEP IS TO SELECT FUNCTIONAL GROUPS TO ATTACH TO THE FRAGMENTS. PRESS ENTER.

LEFT FRAGMENT

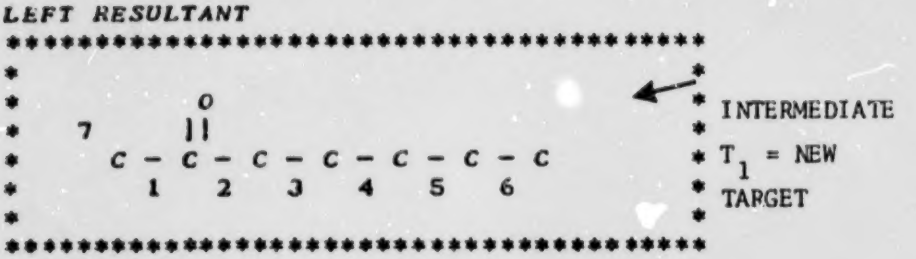


ATTACH FUNCTIONAL GROUP

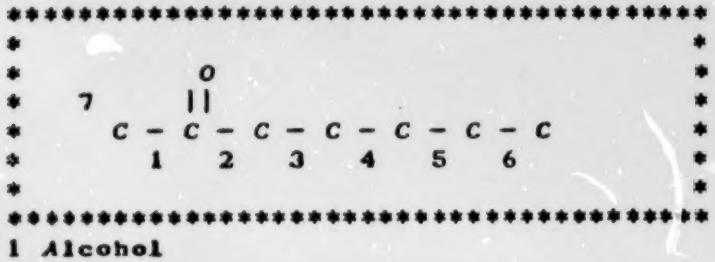
1 Carbonyl
2 Nitrile
3 Carboxylic ester
4 Bromide
5 Hydrogen
6 Grignard
7 Hydroxy

ENTER REAGENT INDEX FROM TABLE FOR -LEFT- FRAGMENT
1
FINE, YOU MUST NOW CHOOSE A REACTION ENVIRONMENT TO PRODUCE THE TARGET FROM THE RESULTANT(S).
PRESS ENTER TO CONTINUE.

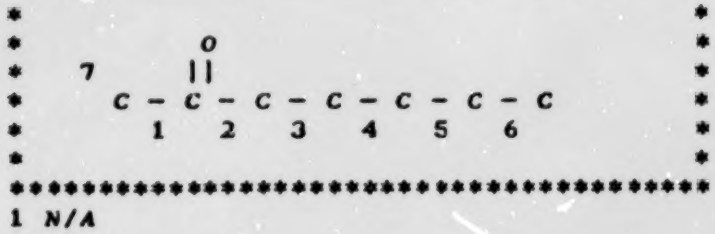
LEFT RESULTANT



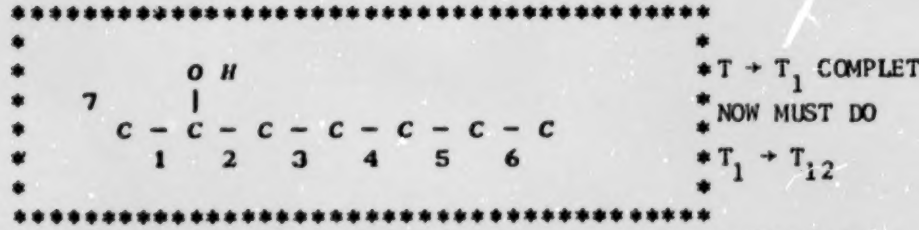
1 *LAH*
2 *Alkoxy base*
3 *Mg turnings*
4 *Nothing*
5 *H3O+*
ENTER THE REAGENT INDEX
1



1 *Alcohol*
2 *Et2O*
3 *Nothing*
ENTER THE SOLVENT INDEX
2



1 *N/A*
2 *RT*
3 *Reflux*
ENTER THE TEMPERATURE INDEX
2
CORRECT, PRESS ENTER



YOU HAVE CORRECTLY PROGRESSED FROM THE TARGET ABOVE TO THE NEW TARGET(S) BELOW. PRESS ENTER TO CONTINUE WITH THE NEW TARGETS.

Results and Discussion

The testing ground for ORGSYN was the Winter, 1978 version of Chemistry 465, a fourth year undergraduate course in organic synthesis. A total of 14 students each completed at least 5 of the 6 programmed syntheses. The instructor was present at all sessions. Printouts of student answers were available for analysis by students and instructor.

Student adaptation to the format of ORGSYN was facilitated by prior exposure to Retrosynthetic Analysis in the classroom. There was visible satisfaction in seeing the presentation of molecular fragment (T_1) after the correct bond had been broken (Fig. 5). Once this was done, the student was committed to a particular synthetic approach which was at least in part several steps beyond T_1 in his mental "tree". Since bond cleavage and selection of a functional group are logically connected, correct response to the latter followed rapidly correct response to the former. As expected, those students who took a "random walk" approach to the cleavage of the correct bond (no mental "tree") had difficulty in selecting the right functional group. In the course of the operation, several ambiguities in functional group listings were noted, e.g. attach "nitrile" (C≡N) resulted in the change of an existing C* in a fragment to a C≡N (i.e. C*≡N) whereas attach "ethoxy-carbonyl" (CO_2Et) led to appending a CO_2Et onto an existing C* (i.e. C* - CO_2Et). Such ambiguities may be corrected by modification of the functional group tables.

The menu tables of Reaction Environment (Fig. 6) was the Dr. Jekyll and Mr. Hyde of ORGSYN. On the "good side", it forced students to think about practical reaction conditions for each retrosynthetic step that they undertook. This led to an increasing awareness for the necessity of rational analysis in the design of organic synthesis. Secondly, it confronted them with the realization that they had largely ignored reaction conditions in previous study of organic chemistry, an unforgivable admission to chemists, engineers, and the discriminate cook! On the "bad side", it was soon discovered that although menu tables were appropriate for the simple syntheses (e.g. Fig. 6), they were ill-defined for the more complex cases. Since menu tables for any given chemical operation contained information which was the sum total of all reagents,

solvents, and temperatures coded in the synthesis of a target molecule, they became long and awkward with the following consequences: a) for a given reaction, several reagents would appear differing little in their chemical properties (Fig. 7). The good student was faced with selecting one of these in a list which contained numerous other choices. The poor student was in a worse position in that he was also tempted by the other choices; b) in the solvent menu, the correct answer " inert solvent" was listed among several other defined solvents (e.g. benzene, ethanol) which could in theory also serve for the reaction under consideration; and c) in the temperature list, lack of definition (N/A = not critically important to the reaction) and over-specification (0°C vs 10°C) provided serious difficulties. All of these problems were compounded by the fact that only one combination of reagent, solvent, and temperature was accepted as the correct answer. Thus a number of students, after several rational approaches to obtain the correct combination, resorted to the "Monte Carlo" method. In tables containing ten or more entries for each of reagents, solvent, and temperature, this approach led to further frustration.

Fig. 7 REACTION ENVIRONMENT

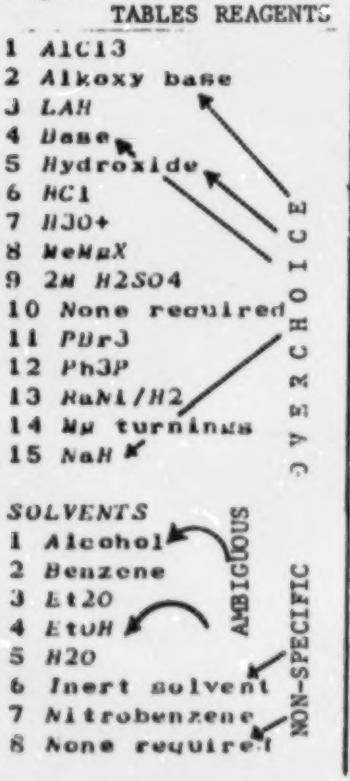
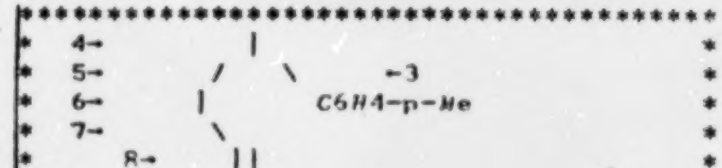


Fig. 8 REACTION ENVIRONMENT




```
BOND CHOSEN WAS: 8
RESPONSE FOR LEFT FRAGMENT: 1 Bromide
REACTION ENVIRONMENT
RESPONSE FOR REAGENT: 12 Ph3P
RESPONSE FOR SOLVENT: 2 Benzene
RESPONSE FOR TEMP:    2 Reflux
SECOND RE
RESPONSE FOR REAGENT: 2 Alkoxy base
RESPONSE FOR SOLVENT: 1 Alcohol
RESPONSE FOR TEMP:    4 R.T.
NO MATCH
RESPONSE FOR REAGENT: 2 Alkoxy base
RESPONSE FOR SOLVENT: 1 Alcohol
RESPONSE FOR TEMP:    1 N/A
NO MATCH
RESPONSE FOR REAGENT: 2 Alkoxy base
RESPONSE FOR SOLVENT: 1 Alcohol
RESPONSE FOR TEMP:    2 Reflux
NO MATCH
```

Judicious pruning of the Reaction Environment tables for excessive information, ambiguities, and lack of specificity will lead to direct solutions of the above problems. Perhaps the greatest difficulty is point a) where it can be envisaged that the requirement for several reagents with very similar chemical behavior cannot be avoided in multi-step synthesis. In such cases, use of separate tables for individual steps rather than the present composite listing presents a potential solution which, however, may not be practical from the computer programming point of view.

The other major difficulty concerns the lack of a feedback mechanism in the Reaction Environment tables which would guide and encourage students rather than promote adoption of the "Monte Carlo" approach (Fig. 8). The solution most beneficial to the student would be the provision of Error and Hint Messages after a NO MATCH result. These could be in the form of questions (e.g. for Solvent: "Have you considered the solubility factor?";for Reagent: "Have you given careful thought to base strength?") or direct statements (e.g. for Temperature: "The high temperature will cause a secondary condensation";for Reagent: "This reagent is not selective for your desired purposed.") After further lack of success (e.g. maximum 3-4 failures) a Giveaway Message would indicate the correct response as well as a reference to a standard text for self-study purposes. This and other potential solutions to the problems encountered in the Reaction Environment tables need to be evaluated from the programming point of view.

Evaluation

By working with the ORGSYN module, students obtained a thorough understanding of the Retrosynthetic Analysis concept. Since this concept was also used in classroom discussions of more complicated molecules, the learning experience in ORGSYN was reinforced (Fig. 9, quote 1). As a result, students developed confidence and elaborated more skilful and imaginative synthetic routes to target molecules posed in regular assignments. ORGSYN had an equally major impact in demonstrating weaknesses in knowledge concerning the Reaction Environment (Fig. 9, quotes 2 and 3). Students became acutely aware of the necessity for judicious choice of conditions in organic transformations.

Fig. 9 STUDENT RESPONSE

1. "... Practice in retrosynthetic chemistry was valuable."
2. "The most important thing I learned was that I was very weak in my knowledge of reaction conditions."
3. "All these years I have ignored solvent and temperature... some organic books do not bother to give conditions....."
4. "It gave me time to work out in my mind what was happening as opposed to the classroom where the information comes thick and fast."
5. "A relatively painless way of learning."

What of the interaction with the computer? Several students responded that it was better than a classroom tutorial allowing greater problem-solving time (Fig. 9, quote 4). Interaction with the instructor was judged to significantly increase progress through a given synthesis. As discussed in the Results and Discussion section, a large part of the human assistance could in theory be programmed. Finally, there appeared to be a definite improvement in learning ability using ORGSYN compared to the classroom. For example, in a normal assignment students failed to recall the function of a particular reagent after it had been mentioned several times in the classroom; yet having been exposed to it once in ORGSYN, the reagent was used correctly in subsequent problem sets. Quote 5, Fig. 9 is a possible explanation for these observations.

Conclusion

The ORGSYN computer-assisted organic synthesis module is successful in meeting objectives 1-3 (Fig. 3). Objectives 4 and 5 have not been adequately tested but may be tentatively answered in the positive on the basis of the student feedback. Due to time limitations, we have not addressed ourselves to objective 6, listed in Fig. 3.

With the initial exposure to the ORGSYN module, the student becomes a more critical and rational analyst, capable of designing organic syntheses of some complexity. ORGSYN should be useful as supplement to lectures and for remedial purposes at several levels of undergraduate organic chemistry instruction.

Acknowledgements

I express my gratitude to John Moore and Jerry Bolce for their patient efforts in overcoming the communication barrier.

References:

[1] A portion of this work is extracted from the M.Sc. thesis of J.A. Oakleaf, University of Waterloo, 1977.

[2] E.J. Corey, Quat. Rev. Chem. Soc., 25, 455 (1971); see also H.W. Orf, J. Chem. Educ., 52, 464 (1975).

[3] S.G. Smith and R. Chabay, J. Chem. Educ., 54, 688 (1977).

[4] H.L. Gelernter et al., Science, 197, 1041 (1977).